

**REMARKS UNDER 37 CFR § 1.116**

**Formal Matters**

Claims 1-8, 10-12 and 15-16 are pending after entry of the amendments set forth herein.

Claims 1-8 and 10-12 were examined. Claims 1-8 and 10-12 were rejected.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

**The Office Action**

In the Official Action of June 30, 2005, claims 1 and 7-8 were rejected under 35 U.S.C. Section 102(b) as being anticipated by Lockhart et al., WO 97/10365. The Examiner asserted that Lockhart et al. discloses a method comprising using an array containing not only oligonucleotide probes referred to as "test probes", but also control probes used for calibration. The Examiner further asserted that, in one embodiment, Lockhart et al. teaches that the difference between signal intensities of a perfect match (PM) probe and a mismatch (MM) probe for each pair of PM and MM are calculated, and then the average of the differences for all the pairs is calculated. The Examiner referred to page 61, first paragraph and page 103, claims 66-67 of Lockhart et al. as support for these assertions.

Upon reviewing page 61, first paragraph of Lockhart et al., Applicants note that Lockhart et al. does not teach averaging the differences for all pair of PM and MM signals, contrary to the Examiner's assertion. Rather, Lockhart et al. discloses, at page 61, lines 2-4, that an average of the difference values for the probes that incremented NPOS and NNEG is calculated. For each pair that exhibits hybridization intensities either indicating that a gene is expressed or not express, a log ratio value (LR) and intensity difference value (IDIF) are calculated. Thus, the average that the Examiner referred to is only computed with respect to those probe pairs (PM and MM) that increment either NPOS or NNEG, and not all probe pairs PM and MM as suggested by the Examiner. For example, If  $I_{pm}=0.8$  and  $I_{mm}=0.6$  with  $D=3$  and  $R=1.5$ , this probe pair would not increment NPOS or NNEG and thus would not be considered when calculating the average of the IDIF values. Claim 1 has been amended above to further clarify this distinction, wherein it has been amended to recite that the collective calibration signal calculated from the signal intensities read from the entire set of calibrating features. Lockhart et al. clearly fails to disclose this feature and actually teaches against the same.

Further, since the total intensities of all MM probes are not calculated for the average, the average does not reflect the total population of the sample solution.

Regarding claims 7-8, Applicants restate that Lockhart et al. does not calculate the average difference for all PM/MM, contrary to the Examiner's assertion, for the reasons explained above. Further, Lockhart et al. calculates an average for only one set, i.e., the set of PM/MM pairs which either incremented NPOS or NNEG. No partitioning is performed as claimed. The calculation for a single PM/MM probe pair does not cover a range, but only a single intensity value.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1 and 7-8 under 35 U.S.C. Section 102(b) as being anticipated by Lockhart et al., WO 97/10365, as being clearly inappropriate.

Claims 1, 3-5, 7-8 and 10-12 were rejected under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1 and 7-8 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Lewin, B., (GENS IV, 1990, Oxford Press University). The Examiner applied essentially the same arguments, regarding Lockhart et al., to these claims as were applied to claims 1, 7 and 8 above. The Examiner asserted that it would be readily recognized by one of skill in the art that when the average difference is calculated, a total intensity of the difference between the PM and MM must have also been calculated, and that, consequently, total intensities of all MM probes are also calculated. Applicants respectfully traverse these assertions, since Lockhart et al. does not calculate a average difference over all PM and MM probes, for the reasons noted above. Nor does Lockhart et al. calculate normalized signal intensities for features that are not in the set of control features based on the signal intensity calculation of the calibration features, where each normalized signal intensity is functionally related to a mole fraction of sample molecules that hybridize to the respective feature.

The Examiner asserted that Chenchik et al. teaches the use of calibration spots and control spots to provide other useful information such as background or basal level of expression, and that one of ordinary skill in the art would have been motivated to apply this teaching to search for probes that are common to the targets in the sample solution to modify Lockhart et al. for proved more calibrating probes for the microarray analysis. However, Chenchik et al. merely discloses the use of orientation marks, which are useful for orienting the grid during feature extraction, and housekeeping genes and negative a positive control genes. These were all discussed in the present specification as standard types of control probes, none of which are used according to the presently claimed methods. The housekeeping genes mentioned by Chenchik are used to determining basal metabolic levels and

background expression levels. There is no teaching in Chenchik et al. of processing signals of the housekeeping genes in the manner that is currently recited in claims 1 and 10. Further, if these housekeeping gene probes were included in the array of Lockhart et al., there is no teaching provided as to how they would be signal processed. Negative control probes, as taught by Chenchik et al., are commonly used for background subtraction purposes, and Chenchik et al. provides no teaching as to their use for normalizing the signal intensities of the mouse gene probes. Nor does Chenchik et al. provide any teaching for using positive control probes for normalizing signal intensities of the mouse gene probes, but only indicates that they can somehow be used to provide other useful information, such as background or basal level of expression. As previously noted, Chenchik et al. does not teach or suggest a normalization procedure based on calibration probes, does not mention or suggest use of average calibration probe intensities, and does not mention use of a normalization function, and therefore is not properly combinable with Lockhart et al. to overcome the deficiencies of Lockhart et al. discussed above.

Nor does Lewin teach or suggest any modifications that would overcome the deficiencies of Lockhart et al. in meeting the recitations of the present claims, since Lewin is merely a textbook reference discussing poly(a) oligonucleotides.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 3-5, 7-8 and 10-12 under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1 and 7-8 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Lewin, B., (GENS IV, 1990, Oxford Press University), as being inappropriate.

Claims 1, 4, 7-8 and 10-12 were rejected under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1 and 7-8 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Darnell et al. (Molecular Cell Biology, Eds., 1990, published by Scientific American Books). The Examiner applied essentially the same arguments, regarding Lockhart et al., to these claims as were applied to claims 1, 7 and 8 above. It is respectfully submitted that this ground of rejection is inappropriate for the same reasons presented above with regard to Lockhart et al. and Chenchik et al., as Darnell et al. is directed only to a description of Alu sequence and does nothing to overcome the deficiencies of Lockhart et al. and Chenchik et al. in meeting the recitations of claims 1 and 10 from which the other claims depend.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 4, 7-8 and 10-12 were rejected under 35 U.S.C.

Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1 and 7-8 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Darnell et al. (Molecular Cell Biology, Eds., 1990, published by Scientific American Books), as being inappropriate.

Claims 1, 6-8 and 10-12 were rejected under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1 and 7-8 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Feinberg et al. (Analytical Biochemistry, Vol. 132, pages 6-13, 1983). The Examiner applied essentially the same arguments, regarding Lockhart et al., to these claims as were applied to claims 1, 7 and 8 above. It is respectfully submitted that this ground of rejection is inappropriate for the same reasons presented above with regard to Lockhart et al. and Chenchik et al., as Feinberg et al. is directed only to a method of labeling DNA by using a mixture of random hexamer as primers. Although the Examiner states that such would have been an ideal probed for use by Chenchik et al., neither Chenchik et al. nor Feinberg et al. teaches or suggests processing an array according to the methods presently claimed. Further, since Lockhart et al. also fails to carry out the method steps claimed for the reasons discussed above, even if these references were properly combinable in the manner suggested by the Examiner, which Applicants respectfully submit that would not be, the resultant combination would still fail to meet the recitations of the present claims, since Lockhart et al. does not calculate the average that was asserted by the Examiner.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 6-8 and 10-12 were rejected under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1 and 7-8 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Feinberg et al. (Analytical Biochemistry, Vol. 132, pages 6-13, 1983), as being inappropriate.

It is respectfully submitted that new claims 15 and 16, presented above, are also allowable over the art of record. Claim 15 depends from claim 1 and, it is respectfully submitted to therefore be allowable for at least the same reasons provided above with regard to claim 1. Further, claim 15 specifies that an average of the signal intensities read from the calibrating features is proportional to the total concentration of target molecules in the sample solution to which the array is exposed. Since neither Lockhart et al., nor any of the other references of record, disclose or suggest calculating such an average, they also fail to calculate an average that is proportional to the total concentration of target molecules in the sample solution.

Claim 16 recites a method for calibrating data scanned from a molecular array, the method comprising: selecting a molecular array that includes a set of calibrating features containing calibrating



probes that hybridize to a sufficient fraction of target molecules of a sample to which the molecular array is intended to be exposed to produce corresponding signal intensities upon reading of the calibrating probes proportional to the total concentration of target molecules in the sample solution, and a set of features containing probes that hybridize to specific target molecules in the sample solution under stringent conditions; exposing the molecular array to a sample solution; determining a mole fraction of sample molecules that hybridize to the calibration features; and calculating normalized signal intensity of a feature containing probes that hybridize to a specific target molecule, based on a mole fraction of the sample molecules that hybridize to the feature containing probes that hybridize to a specific target molecule and the mole fraction of sample molecules that hybridize to the calibration features. Clearly none of the prior art discloses or suggests these features.

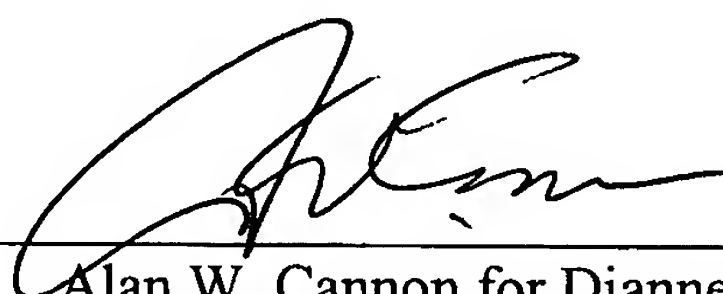
### Conclusion

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10020405-1.

Respectfully submitted,  
Wolber et al.

Date: 8/30/2005

By:   
Alan W. Cannon for Dianne Rees  
Registration No. 34,977

Dianne Rees  
Agilent Technologies, Inc.  
Legal Department, DL429  
Intellectual Property Administration  
P.O. Box 7599  
Loveland, CO 80537-0599  
Telephone: (650) 485-5999  
Facsimile: (650) 485-5487